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## Association of Obesity with Disease Severity among Patients with COVID-19

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**Running title:** Obesity association with COVID-19 severe outcomes

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**Authors' contributions:** Author contributions: All authors conceptualized and designed the study, and participated in data interpretation. MK and FS participated in data collection and extraction. MK, FS and EKM prepared tables and performed the statistical analysis. MK, FS, EKM and GB drafted the initial manuscript. All authors reviewed and revised the manuscript. All authors read and approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Abbreviations:** **BMI:** Body Mass Index, **CI:** Confidence interval, **COVID-19:** Coronavirus Disease 2019, **ICU:** Intensive Care Unit, **IMV:** Invasive Mechanical Ventilation, **IQR:** Interquartile Range, **OR:** Odds Ratio

### Study Importance

What is already known about this subject?

- Chronic conditions like diabetes, hypertension, obesity, heart and lung disease, have been associated with COVID-19 severity.
- Evidence is limited and the extent of these associations is not fully understood.

What are the new findings in this study?

- This US study shows that heart disease and obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) are independently associated with the use of invasive mechanical ventilation in patients with COVID-19.

How might these results change the direction of research or the focus of clinical practice?

- Individuals with  $\text{BMI} \geq 35 \text{ kg/m}^2$ , and especially those with heart disease, are at high risk for severe COVID-19
- In areas with high prevalence of obesity, these findings can have significant impact in the triaging and evaluation of patients.
- Studies should focus on mechanisms that explain why obesity is associated with increased COVID-19 severity, as well as streamlined prevention and treatment strategies for these patients.

## Abstract

**Objective:** To explore the potential association of obesity and other chronic diseases with severe outcomes, such as intensive care unit (ICU) admission and invasive mechanical ventilation (IMV), in patients hospitalized with COVID-19.

**Methods:** Retrospective cohort of 103 patients hospitalized with COVID-19. Demographic data, past medical history and hospital course were collected and analyzed. A multivariate logistic regression analysis was implemented to examine associations.

**Results:** From February 17th to April 5th, 103 consecutive patients were hospitalized with COVID-19. Among them, 41 patients (39.8%) were admitted to the ICU and 29 (70.7%) required (IMV). The prevalence of obesity was 47.5% (49/103). In a multivariate analysis, severe obesity (BMI  $\geq 35$  kg/m<sup>2</sup>) was associated with ICU admission (aOR 5.39; 95% CI:1.13-25.64). Moreover, patients who required IMV, were more likely to have had heart disease (aOR 3.41; 95% CI:1.05-11.06), obesity (BMI=30-34.9 kg/m<sup>2</sup>) (aOR 6.85; 95% CI: 1.05-44.82) or severe obesity (BMI $\geq 35$  kg/m<sup>2</sup>) (aOR 9.99; 95% CI:1.39-71.69).

**Conclusion:** In our analysis, severe obesity (BMI  $\geq 35$  kg/m<sup>2</sup>) was associated with ICU admission, while history of heart disease and obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) were independently associated with the use of IMV. Increased vigilance and aggressive treatment of patients with obesity and COVID-19 are warranted.

# 1.Introduction

In late December 2019, a cluster of patients with pneumonia of unknown origin was first reported in Wuhan, China [1]. Since then, Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has taken the world by storm and was officially declared a pandemic by the World Health Organization on March 11, 2020. Clinical manifestations of COVID-19 range from asymptomatic or mild infection to severe forms of disease that are life-threatening. Among other risk factors, chronic conditions such as chronic lung disease, cardiovascular disease, diabetes mellitus, and hypertension [2-4], seem to increase the risk for severe COVID-19 outcomes. In addition, although the role of obesity was initially neglected [5], recent reports [6, 7] found that obesity is associated with severe COVID-19 outcomes as well.

In this study we utilize data from the largest healthcare network in Rhode Island, USA, with the aim of exploring the potential association of the above-mentioned chronic diseases with severe outcomes such as ICU admission and invasive mechanical ventilation (IMV) in patients hospitalized with SARS-CoV-2 infection.

## 2. Methods

### 2.1 Study Design and Patient Selection

All consecutive adult ( $\geq 18$  years old) patients, who had a laboratory confirmed (using a reverse transcriptase–polymerase chain reaction assay) SARS-Cov-2 infection and were admitted to Rhode Island Hospital, The Miriam Hospital, or Newport Hospital, in Rhode Island, USA, between February 17<sup>th</sup> and April 5<sup>th</sup>, 2020 were considered eligible for inclusion. This study was a retrospective electronic chart review and it was approved by the Institutional Review Board of Rhode Island Hospital. A consent waiver was also obtained for the purposes of this study. This retrospective cohort study was performed in line with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement (Table S1).

### 2.2 Data Collection

Two independent investigators (MK, FS) extracted deidentified demographic, epidemiological, clinical and laboratory data of interest. More specifically, we extracted the following variables: age, gender, race, smoking status, body mass index (BMI), past medical history and hospitalization course.

### 2.3 Study outcomes

Our primary outcome was to assess if specific risk factors, namely age, race, gender, BMI, diabetes, hypertension, chronic heart disease, and chronic lung disease are associated with ICU-admission within the first 10 days of hospital admission with COVID-19. Our secondary objective was to assess if the aforementioned factors are associated with the need for IMV during the first 10 days of hospital admission with COVID-19.

#### *2.4 Statistical Analysis*

For the purposes of statistical analysis, we represented continuous measurements as medians (IQRs) and we compared them using the Mann-Whitney-Wilcoxon test. For categorical data, we used a two-proportion z-test to compare the difference in population proportions between patients admitted to the ICU and patients that did not require ICU admission. We also examined the association of ICU admission and the need for IMV with the following variables: age, race, gender, BMI, diabetes, hypertension, heart disease, and chronic lung disease. After examining the associations in a univariate logistic regression model, we performed multivariate logistic regression analysis, where we included all of the above-mentioned variables in the same model. In addition, for the outcome of obesity we show a model that adjusts for potential demographic confounders, but does not include the other chronic disease variables. For our analyses 95% confidence intervals and *P*-values are shown. All analyses were performed using Stata v15.1 (Stata Corporation, College Station, TX).

### **3. Results**

We identified 103 adult consecutive patients who were admitted with COVID-19 in our hospitals from February 17<sup>th</sup> to April 5<sup>th</sup>. Patients baseline characteristics are depicted on Table 1. The median age of patients was 60 (52-70) years, while 63 patients (61.17%) were men. Among hospitalized patients with COVID-19, 42 were Non-Hispanic White, 35 were Hispanic, 24 were Non-Hispanic Black and 2 were Non-Hispanic Asian. The most common comorbidities were hypertension (64%), followed by diabetes (36.8%) and heart disease (24.2%). The prevalence of obesity was 47.5% among hospitalized patients, 56.8% among patients requiring ICU admission and 65.5% among patients who required IMV. During the first 10 days of their hospitalization, 41 out of 103 patients were admitted to the ICU and 29 of them required IMV.

Both univariate and multivariate logistic regression analyses were used to examine the association of variables with ICU admission within the first 10 days of hospital admission (Table 2). In univariate models none of the variables was associated with ICU admission. We performed a multivariate analysis (adjusted for age, gender and race) to examine the association of obesity

with ICU admission and found that severe obesity ( $\geq 35$  kg/m<sup>2</sup>) was associated with increased risk of ICU admission (aOR 6.16; 95% CI:1.42-26.66). We then extended our multivariate model to include 4 additional chronic diseases. Although diabetes, heart disease and lung disease seemed to increase the risk of ICU admission, only severe obesity ( $\geq 35$  kg/m<sup>2</sup>) reached statistical significance (aOR 5.39; 95% CI:1.13-25.64).

As a secondary outcome we examined factors associated with IMV within 10 days of hospital admission with COVID-19 (Table 3). In univariate models, preexisting heart disease and severe obesity were associated with the need for IMV. In a multivariate model examining the association of different BMI categories with IMV (after adjusting for age, gender and race), severe obesity ( $\geq 35$  kg/m<sup>2</sup>) was associated with need for IMV (aOR 8.19; 95% CI:1.36-49.13). In our expanded multivariate model, even though diabetes was associated with a trend for IMV, only heart disease and obesity reached statistical significance. More specifically, patients who needed IMV were more likely to have had a diagnosis of preexisting heart disease (aOR 3.41; 95% CI: 1.05-11.06), or obesity (aOR of 6.85 and 9.99 for BMI 30-34.9 and  $\geq 35$  kg/m<sup>2</sup>, respectively).

#### **4. Discussion**

We report one of the first US cohorts that investigates the association of obesity with the severity of COVID-19. We found that severe obesity (BMI  $\geq 35$  kg/m<sup>2</sup>) was associated with ICU admission, while history of heart disease and obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) were independently associated with the use of IMV. A disproportionate impact of COVID-19 on patients with obesity should be anticipated since it has also been previously documented for different viral pathogens including influenza [8-10]. Particularly, rates of hospitalizations and death due to the H1N1 influenza virus during the 2009 H1N1 pandemic were greater for adults with both obesity and morbid obesity [11]. Of note, death was associated with obesity (OR 3.1; 95% CI: 1.5-6.6) and morbid obesity (OR 7.6; 95% CI 2.1-27.9) even in patients who had no history of other medical conditions.

Given that the epicenters of COVID-19 are now North America and Europe, the impact of obesity on COVID-19 outcomes might become even more pronounced, since these two continents have the highest prevalence of obesity globally [12]. Relatedly, the first results from France [7] and New York [6] are in concordance with our findings and confirm this hypothesis. In a retrospective cohort study with 124 patients from France, Simonnet et al. found that obesity prevalence was high among ICU admitted patients (47.6%), while the aOR for IMV in patients with BMI  $\geq 35$  kg/m<sup>2</sup>, compared to patients with normal weight, was 7.36 (1.63-33.14). Similarly, a study from New York with 3615 patients by Lighter et al., yielded that compared to individuals

with a BMI <30, patients with a BMI between 30-34.9 were 2.0 and 1.8 times more likely to be admitted to acute and critical care, respectively [6].

Although the exact mechanism by which obesity may contribute to severe COVID-19 outcomes is not yet defined, several parameters may play a role. First, patients with obesity have altered respiratory physiology, including decreased functional residual capacity and expiratory reserve volume, as well as hypoxemia and ventilation/perfusion abnormalities [13]. In addition, obesity has been associated with impaired immune system surveillance and response [14], while the levels of ACE2 enzyme expression in adipose tissue, an enzyme for which SARS-CoV-2 shows high affinity, may also play a role and need to be further studied [15].

Interestingly, we also found an association between preexisting heart disease (which is often associated with obesity as well [16]) and the need for IMV. Such findings, are in agreement with previous reports which mentioned that patients with cardiovascular diseases had an increased risk for severe outcomes, including death from COVID-19 [17]. We should also mention that although chronic diseases like diabetes did not reach statistical significance in our analysis, previous reports have found an association with worse COVID-19 outcomes [18]. Thus, future studies with more patients should reassess these findings.

Our study has some limitations that should be taken into consideration. Our confidence intervals were relatively wide, likely because of the small sample size. In addition, there was low statistical power for testing interactions. Although the retrospective cohort study design used can estimate associations only; similar to a prospective design, our study does have the strength of certainty in regard to the temporal sequence of the exposures and outcomes.

In conclusion, our findings emphasize the need for early detection and aggressive treatment for patients with obesity and COVID-19, especially in countries like the US, where the prevalence of obesity is over 40% [19]. We highlight the need for future studies which will assess the mechanisms behind increased COVID-19 severity in patients with obesity, as well as the need for streamlined prevention and treatment strategies for these patients.

## Declarations

**Ethics approval and consent to participate:** The study was approved by the Rhode Island Hospital IRB.

**Consent for publication:** Not applicable

**Availability of data and materials:** The datasets generated and/or analyzed during the current study are not publicly available due to HIPAA restrictions. De-identified summary data are available from the corresponding author on reasonable request.

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## Tables

**Table 1. Baseline Characteristics of patients hospitalized with COVID-19**

	All (n=103)	ICU admitted (n=44)	Non-ICU (n=59)
Age	60 (50-72)	61.5 (54.5-72.5)	57 (48-72)
Male	63 (61.1%)	29 (65.9%)	34 (57.6%)
Non-Hispanic White	42 (40.7%)	20 (45.4%)	22 (37.2%)
Non-Hispanic Black	24 (23.3%)	11 (25.0%)	13 (22.0%)
Hispanic	35 (33.9%)	12 (27.2%)	23 (38.9%)
Non-Hispanic Asian	2 (1.9%)	1 (2.2%)	1 (1.6%)
Active Smoker	12 (11.7%)	3 (6.8%)	9 (15.25%)
Former Smoker	36 (34.9%)	17 (38.6%)	19 (32.2%)
Never Smoker	55 (53.4%)	24 (54.5%)	31 (52.5%)
BMI <25	19 (18.4%)	5 (11.3%)	14 (23.7%)
BMI 25-29.9	35 (33.9%)	14 (31.8%)	21 (35.5%)
BMI 30-34.9	22 (21.3%)	11 (25.0%)	11 (18.6%)
BMI ≥35	27 (26.2%)	14 (31.8%)	13 (22.0%)
<b>Comorbidities</b>			
Cancer	9 (8.7%)	6 (13.6%)	3 (5.0%)
Chronic Renal	11 (10.6%)	4 (9.1%)	7 (11.8%)
Cirrhosis	3 (2.9%)	0	3 (5.0%)
Diabetes*	38 (36.8%)	21 (47.7%)	17 (28.8%)
Heart Disease	25 (24.2%)	14 (31.8%)	11 (18.6%)
Hypertension	66 (64.0%)	31 (70.4%)	35 (59.3%)
Lung Disease	20 (19.4%)	11 (25.0%)	9 (15.2%)
Transplant	2 (1.9%)	1 (2.2%)	1 (1.6%)

Continuous: Median (IQR), Categorical: N (%), BMI: body mass index (kg/m<sup>2</sup>), \* p-value =0.025

Heart Disease: heart failure, coronary artery disease, cardiomyopathy,

Lung Disease: COPD, asthma, interstitial lung disease, pulmonary hypertension

**Table 2. Association of different variables with ICU admission within 10 days of hospital admission with COVID-19**

	<i>Univariate</i>		<i>Multivariate<sup>1</sup></i>		<i>Multivariate<sup>2</sup></i>	
	OR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Age	1.02 (1.00-1.05)	0.067	1.03 (1.00-1.07)	0.016	1.03 (1.00-1.07)	0.059
Non-Hispanic White	ref		ref		ref	
Non-Hispanic Black	0.93 (0.34-2.54)	0.889	0.86(0.29-2.56)	0.797	0.80 (0.26-2.45)	0.701
Hispanic	0.57 (0.23-1.45)	0.239	0.65 (0.24-1.76)	0.402	0.56 (0.19-1.58)	0.271
Female	ref		ref		ref	
Male	1.42 (0.63-3.19)	0.394	2.24 (0.86-5.78)	0.095	2.40 (0.87-6.64)	0.09
BMI <25	ref		ref		ref	
BMI 25-29.9	1.87 (0.55-6.35)	0.318	2.14 (0.58-7.88)	0.250	2.27 (0.59-8.83)	0.235
BMI 30-34.9	2.80 (0.75-10.48)	0.126	2.56 (0.64-10.1)	0.100	2.65 (0.64-10.95)	0.178
BMI ≥35	3.02 (0.85-10.74)	0.088	<b>6.16 (1.42-26.66)</b>	<b>0.015</b>	<b>5.39 (1.13-25.64)</b>	<b>0.034</b>
Diabetes	2.26 (1.00-5.11)	0.051	-	-	1.91 (0.71-5.19)	0.202
Hypertension	1.64 (0.71-3.75)	0.246	-	-	0.79 (0.27-2.28)	0.663
Heart Disease	2.04 (0.82-5.07)	0.126	-	-	1.52 (0.51-4.51)	0.448
Lung Disease	1.85 (0.69-4.96)	0.22	-	-	1.50 (0.47-4.82)	0.495

*BMI: body mass index (kg/m<sup>2</sup>),*

*Heart Disease: heart failure, coronary artery disease and cardiomyopathy, Lung Disease: COPD, asthma, interstitial lung disease and pulmonary hypertension*

<sup>1</sup>*Adjusted for Age, Race, Gender*

<sup>2</sup>*Fully Adjusted*

**Table 3. Association of different variables with the need for invasive mechanical ventilation within 10 days of hospital admission with COVID-19**

	<i>Univariate</i>		<i>Multivariate<sup>1</sup></i>		<i>Multivariate<sup>2</sup></i>	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.01 (0.98-1.04)	0.454	1.02 (0.99-1.06)	0.129	1.02 (0.98-1.06)	0.271
Non-Hispanic White	ref		ref		ref	
Non-Hispanic Black	1.92 (0.65-5.71)	0.241	2.02 (0.63-6.47)	0.234	1.83 (0.55-6.11)	0.327
Hispanic	1.28 (0.46-3.55)	0.636	1.58 (0.53-4.74)	0.407	1.17 (0.36-3.82)	0.796
Female	ref		ref		ref	
Male	1.05 (0.44-2.55)	0.906	1.18 (0.43-3.19)	0.744	1.13 (0.32-3.40)	0.825
BMI <25	ref		ref		ref	
BMI 25-29.9	2.52 (0.48-13.30)	0.277	2.64 (0.48-14.4)	0.262	3.70 (0.60-22.87)	0.159
BMI 30-34.9	4.86 (0.88-26.68)	0.069	5.28 (0.91-30.48)	0.063	<b>6.85 (1.05-44.82)</b>	<b>0.045</b>
BMI ≥35	<b>5.84 (1.12-30.55)</b>	<b>0.036</b>	<b>8.19 (1.36-49.13)</b>	<b>0.021</b>	<b>9.99 (1.39-71.69)</b>	<b>0.022</b>
Diabetes	2.38 (0.99-5.72)	0.054	-	-	2.13 (0.73-6.22)	0.168
Hypertension	1.35 (0.54-3.38)	0.518	-	-	0.47 (0.13-1.66)	0.242
Heart Disease	<b>3.31 (1.28-8.57)</b>	<b>0.014</b>	-	-	<b>3.41 (1.05-11.06)</b>	<b>0.041</b>
Lung Disease	1.49 (0.52-4.22)	0.45	-	-	0.76 (0.20-2.86)	0.687

*BMI: body mass index (kg/m<sup>2</sup>),*

*Heart Disease: heart failure, coronary artery disease and cardiomyopathy, Lung Disease: COPD, asthma, interstitial lung disease and pulmonary hypertension*

<sup>1</sup>*Adjusted for Age, Race, Gender*

<sup>2</sup>*Fully Adjusted*